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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/927,933	08/13/2001	Pierre Leroy	032751-066	6916

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EXAMINER	
PRIEBE, SCOTT DAVID	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/06/2003

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/927,933	LEROY ET AL.	
	Examiner	Art Unit	
	Scott D. Priebe	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2003* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *40-44 and 46-60* is/are pending in the application.

4a) Of the above claim(s) *42* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *40,41,43,44 and 46-60* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *4* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Information Disclosure Statement

The information disclosure statement filed 8/13/01 fails to comply with 37 CFR 1.98(a)(3) because it does not include a concise explanation of the relevance, as it is presently understood by the individual designated in 37 CFR 1.56(c) most knowledgeable about the content of the information, of each patent listed that is not in the English language. FR 2706486 has been placed in the application file, but the information referred to therein has not been considered.

Applicant's arguments filed 7/21/03 have been fully considered but they are not persuasive. Applicant argues that the International Search Report filed in the parent application includes a concise statement regarding the relevance of this document. However, the International Search Report only cites the document and indicates those claims of the PCT application to which the document was relevant. It does not identify any part of the French patent that was deemed relevant to the PCT claims, and the PCT claims were in French. Consequently, the Search Report does not contain the concise explanation of the relevance required under 37 CFR 1.98(a)(3).

Election/Restrictions

This application contains claim 42, in its entirety, and claims 40, 41, 43-48, and 51-60 as directed to other than a CD4-antibody fusion drawn to an invention nonelected with traverse in Paper No. 13, filed 2/28/03. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Applicant's comments (pages 20-21) regarding the restriction requirement are noted. However, since the restriction requirement had been made final, further traversal is misplaced, and the comments have not been considered. See MPEP 821.

Inventorship

In view of the papers filed 6/10/02, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by addition of Majid Mehtali.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of the file jacket and PTO PALM data to reflect the inventorship as corrected.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The following title is suggested: .

-- Adenoviral vectors encoding an antibody fused to a CD4 extracellular domain --

Applicant's comments are noted, however, the current title is not descriptive when considering either the claimed subject matter in general or the elected subject matter in particular.

Claim Objections

Claims 40, 41, 43-48, and 51-60 are objected to because of the following informalities: These claims embrace non-elected inventions or species, and should be amended to reflect the election, which has been made final. Appropriate correction is required.

Claim Rejections - 35 USC § 112

Claims 48-50 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims require nucleotide sequences encoding heavy and light chains of the 2F5 monoclonal antibody. The application discloses an exogenous nucleotide sequences encoding heavy and light chains of the 2F5 monoclonal antibody that is encompassed by the definitions for **biological material** set forth in 37 C.F.R. § 1.801. Because it is apparent that this biological material is essential for practicing the claimed invention since the sequence are recited in claims 48 and 49, it must be obtainable by a reproducible method set forth in the specification or otherwise be known and readily available to the public as detailed in 37 C.F.R. §§ 1.801 through 1.809. The specification indicates that the source of these nucleotide sequences are either the 2F5 hybridoma or plasmids pTG2676 (light chain) and pTG2677 (heavy chain). While the

specification discloses primers that could be used to produce the nucleotide sequences by PCR from either the hybridoma mRNA or the plasmids, it does not provide the sequence of these nucleotide sequences. Consequently, the only reproducible method disclosed requires either the hybridoma or the plasmids as a source of template nucleotide sequences.

It is unclear whether the hybridoma or plasmids are known and readily available to the public or that the written instructions are sufficient to reproducibly construct this biological material from starting materials known and readily available to the public. Accordingly, availability of such biological material is deemed necessary to satisfy the enablement provisions of 35 U.S.C. § 112. If this biological material is not obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological material, either of the hybridoma or of plasmids pTG2676 and pTG2677. In order for a deposit to meet all criteria set forth in 37 C.F.R. §§ 1.801-1.809, applicants or assignee must provide assurance of compliance with provisions of 37 C.F.R. §§ 1.801-1.809; in the form of a declaration or applicant's representative must provide a statement. The content of such a declaration or statement is suggested by the enclosed attachment. Because such deposit will not have been made prior to the effective filing date of the instant application, applicant is required to submit a verified statement from a person in a position to corroborate the fact, which states that the biological material which has been deposited is the biological material specifically identified in the application as filed (37 C.F.R. § 1.804). Such a statement need not be verified if the person is an agent or attorney registered to practice before the Office. Applicant is also reminded that the specification must contain reference to the deposit, including deposit (accession) number, date of deposit, name and address of the depository, and the complete taxonomic description.

Applicant's arguments filed 7/21/03 have been fully considered but they are not persuasive. Exhibits A, B, and C are all patents that issued well after the effective filing date of the instant application, and cannot be used here by Applicant to show what was known generally to "any person skilled in the art," to quote from § 112. *In re Glass*, 181 USPQ 31, 34 (CCPA 1974). Indeed, the 2F5 hybridoma is the claimed invention of Exhibit A, and need not have been made publicly available until issue. None of the exhibits provide evidence that at the time the instant invention was made, either the 2F5 hybridoma was publicly available, or the amino acid sequence of the 2F5 monoclonal antibody was known.

Claims 48 and 60 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

New claim 48 is directed to the adenoviral vector of claim 40 wherein the antibody is the 2F5 antibody specifically, which is fused to a generic toxic substance or generic immunopotentiating substance and without limitation as to where on the antibody either substance is fused. New claim 60 is directed to an adenoviral vector where the antibody is fused to both a generic toxic substance and generic immunopotentiating substance, rather than a toxic substance or an immunopotentiating substance, as recited in claim 40 and as generally described throughout the specification.

Applicant has pointed to page 10, lines 4-20, as support for claim 40. However, this does not mention 2F5 at all, and simply describes the order of fusion of different parts of a modified antibody. Applicant has pointed to page 13, lines 21-36, as support for claim 60. However, this describes a retroviral vector comprising a specific exogenous nucleotide sequence encoding the specific fusion protein recited in claim 50.

An adenoviral vector comprising a more general exogenous nucleotide sequence encoding fusion protein recited in claim 50 is disclosed elsewhere in the specification, e.g. page 18 and original claim 28. This specific fusion protein is the only species readable on claim 60 that is disclosed. The only originally disclosed species readable on claim 48 are those recited in claims 49 and 50 (see e.g. original claims 27 and 28). The specification also describes an adenoviral vector expressing unmodified 2F5, but this species is not readable on claim 48.

There does not appear to be support in the original specification for a vector, adenoviral or otherwise, expressing the generic fusion proteins recited in claims 48 or 60, nor has Applicant indicated any such support for these genera. The original specification does not describe embodiments where a generic toxic or immunopotentiating substance is fused to the 2F5 antibody or in any possible arrangement, nor does it describe a generic modified antibody comprising both a generic toxic substance and generic immunopotentiating substance. One cannot pick and choose among characteristics of a specific example in hindsight, and then use the chosen characteristic as the basis of a generic claim. Single species rarely, if ever, provide support for a generic claim, as Applicant is attempting here, especially where such generic claims embrace virtually limitless species, as is the case here. *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481 (CAFC 2000); *In re Shokal,* 113 USPQ 283 (CCPA 1957).

Claim Rejections - 35 USC § 102 & 103

Claims 44, 57, and 58 remain and claim 59 is rejected under 35 U.S.C. 102(b) as being clearly anticipated by Kolls et al. (Proc. Natl. Acad. Sci. USA 91: 215-219, Jan. 1994) for the reasons of record set forth in the Office action of 3/25/03.

Applicant's arguments filed 7/21/03 have been fully considered but they are not persuasive. First, the rejection is properly made under 35 U.S.C. 102(b), Kolls was published more than one year prior to the date of application for a patent in the U.S., i.e. PCT/FR95/ 01171 filed 9/13/1995. The filing of the French priority application is not relevant here. Second, in response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., no toxic or immunopotentiating substance) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). It is further pointed out, that "immunopotentiating" is not defined in the specification as enhancement of an immune response against something. An immune suppression may also be potentiated, and that is the function of the soluble TNF in Koll. It increases suppression of immune response against the adenoviral infected cells above that provided by the E3 region present on the adenoviral vector. The rejection of claim 40 and its dependent claims is withdrawn because Koll does not teach that the antibody is one directed against a tumor cell or epitope of an infectious or pathogenic agent.

Claims 40, 41, 43, 44, 46, 47, 51-59 are rejected under 35 U.S.C. 102(b) as anticipated by or, in the alternative, under 35 U.S.C. 103(a) as obvious over Fell, Jr. et al. US 5,314,995, as evidenced by Berkner, K.L. (Curr. Top. Microbiol. Immunol. 158: 39-66).

Fell, Jr. discloses vectors, including adenoviral vectors (col. 6, lines 38-50), that encode a modified heavy chain of an antibody comprising an immunopotentiating substance, e.g. IL-1, IL-2, an interferon, or chemotactic factor, or a toxic substance, e.g. IL-2 or platelet factor-4 (for anti-angiogenesis of tumor) fused to the carboxy terminus of the heavy chain (col. 3, line 62 to col. 4, line 23; col. 8; col. 9-12; and accompanying figures). The antibody is one directed against a tumor (col. 3, lines 38-61; col. 7, line 60 to col. 8, line 28) or antigens of infectious agents (col. 8, lines 29-36). The nucleic acids encoding the modified antibody are operably linked to one of an SV40 early promoter, RSV promoter, PGK promoter, or α-feto-protein promoter (tumor specific) (col. 5). The vectors are used for *in vitro* production of the modified antibodies from infected cells, which are heteromers of modified heavy and light chains, i.e. the modified heavy chain is "capable of forming a multimer", in this case a heterotetramer.

Fell, Jr. does not explicitly state that the adenoviral vectors are derived from human adenovirus or that they are replication defective. However, Berkner discloses that at the time Fell, Jr. was filed, the only adenoviral vectors that were available, e.g. for *in vitro* expression, were based on human adenovirus, primarily Ad5, but also Ad2, Ad4 and Ad7. Furthermore, Berkner discloses that both replication competent, and replication deficient (specifically, by deletion of all or part of E1) adenoviral vectors had been used (pages 47-55). Consequently, one of skill in the art before the instant invention was made would have been aware that the adenoviral vectors of Fell, Jr. were derived from human adenovirus, and could be either

replication-competent or defective. The term "pharmaceutical" recited in claim 54, for example, refers to an intended use for an adenovirus composition, which does not distinguish the composition from one that would be used in cell culture for example.

Claims 44, 57, and 58 remain and claim 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Allaway et al. (WO 94/19017) in view of Berkner (WO 90/01550) for the reasons of record set forth in the Office action of 3/25/03.

Applicant's arguments filed 7/21/03 have been fully considered but they are not persuasive. First of all, none of claims 44, 57, 58, and 59 require an antibody, much less one that is directed to a tumor cell or pathogen. Second, Berkner explicitly discloses that the multimeric protein encoded by the adenovirus include immunoglobulins. In response to applicant's arguments against the Berkner for not teaching antibody fusion proteins, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Applicant also asserts that one would not have had a reasonable expectation of success "of creating therapeutic quantities of complex multimeric proteins", apparently because Berkner does not provide working examples of expression of multimeric proteins. Applicant also alleges "difficulties inherent in such an undertaking" but fails to identify what those difficulties are, or how they would prevent one from carrying out the combined teachings. Many undertakings in molecular biology are difficult, and require the high level of skill found in this art. Also, none of the claims are directed to "therapeutic quantities of complex multimeric proteins" or to methods of making such, the

claims are directed to adenoviral vectors. Consequently, this argument is irrelevant to the rejection.

Allowable Subject Matter

Claims 49 and 50 would be allowable if rewritten to include all of the limitations of the base claim and any intervening claims, and if a suitable biological deposit were made to overcome the rejection of these claims under 35 USC 112, first para.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Scott D. Priebe whose telephone number is (703) 308-7310. The examiner can normally be reached on M-F, 8:00-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Reynolds can be reached on 703 305-4051. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Scott D. Priebe
Primary Examiner
Art Unit 1632